MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE May 5, 1997

FROM Patricia E. Hasemann, Bioresearch Monitoring, HFM-650
Division of Inspections and Surveillance

SUBJECT Bioresearch Monitoring Inspection Results
BLA 97-1251
Product: Simulect (SDZ CHI 621, basiliximab)
Sponsor: Novartis Pharmaceuticals Corporation

TO Dr. Frederick W. Miller, HFM-561
Chair, BLA Licensing Committee

Summary Statement

This report includes all inspection information available as of this date. The results of the bioresearch monitoring inspections of 3 clinical sites indicate that the submitted data from the studies, with the exceptions noted, can be considered reliable and accurately reported.

Background

This multicenter trial performed under protocol CHIB 352-E-00 was conducted at 21 centers in the United States between June 13, 1995, and May 5, 1997, with a total of 348 subjects enrolled. Inspections of 3 clinical sites were requested in support of BLA 97-1251. The inspections were conducted in accordance with FDA's Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The inspected sites had a total of 119 subjects enrolled representing 34% of the total subject population.

Copies of sponsor submitted study data for each subject enrolled in the selected study sites were obtained from the BLA and provided with the inspection assignments for data comparison. The assignment included specific questions concerning the study.

Study Title: Protocol CHIB 352-E-00: A Multicenter, Randomized, Double-Blind, Placebo Controlled Trial of SDZ CHI 621 for the Prevention of Acute Cellular Rejection in Renal Allograft Recipients

Data audits were performed at the following clinical trial sites:

Dr. William Bennett — Center —— Subjects
Oregon Health Sciences University
Portland, OR 97201-3098

Dr. Barry D. Kahan — Center ——Subjects
University of Texas Medical School at Houston
Houston, TX 77030

Dr. P. R. Rajagopalan — Center —— Subjects
Medical University of South Carolina
Charleston, SC 29425

Inspectional Findings

Dr. Bennett

Records were reviewed for 14 subjects enrolled at this site. The records for all the audited subjects revealed that they received the proper dosage of the trial drug on days 0 and 4 of the study. A protocol deviation as discussed below was noted for the duration of infusion in 1 subject. The study site received approval from the sponsor to use the Oregon Health Services University routine steroid immunosuppression induction regimen (——— treatment of rejection) which differed from the steroid regimen specified in the protocol.

A comparison of sponsor submitted immunosuppressive therapy with data audited at the study site indicated that the sponsor information was primarily accurate and no specific discrepancies were documented in the Establishment Inspection Report (EIR) although the report states that some apparent variation was observed between the daily dosing quantities of immunosuppressive medications reported by the sponsor and those calculated from study site source data which in some cases appeared to be lower amounts than those reported by the sponsor. Comparison of subject records with sponsor submitted study data for acute rejection episodes/treatment, graft losses, subject deaths, adverse events, laboratory variables, vital signs, infections and neoplasms noted no discrepancies.

Deviations noted from the regulations are as follows:

1. Failure to maintain control of the investigational drug. [21 CFR 312.61]

   One dose of the investigational drug was administered to one non-study cadaveric renal transplant patient (—— because a pharmacist thought that all transplant patients were participating in the study.

The error was reported to the sponsor and the patient's treatment was unblinded. As a result of this incident, the study site medication dispensing procedures were updated to prohibit this type of error in the future.

2. Failure to ensure that an investigation is conducted according to the signed investigational plan (protocol). [21 CFR 312.60]

   Subject — placebo) was administered the first dose of study medication in 4 minutes rather than the required 20-30 minutes specified in the protocol.

Dr. Kahan

Records were reviewed for 12 subjects enrolled at this site. Data was verified for rejection episodes (compared with pathology reports), graft loss summaries, adverse reactions, laboratory results, vital signs, infections and neoplasms with no discrepancies observed between the sponsor submitted study data and the subject records on site. The subjects' hospital records and case report forms indicate that the study drug was administered at the required dose at proper intervals. No deaths were reported for any subjects during the study period. Minor deficiencies noted during the inspection included failure of study subjects to return empty Neoral containers (90% of subjects audited did not return any containers) and laboratory results for 1 subject — signed as reviewed by the study coordinator. Three subjects did not return for several of the last visits but are listed by the sponsor as completing the study. Subject — was not seen beyond week 38, subject —did not return after week 42, and subject — graft loss) did not return after week 28. According to the study coordinator who contacted the sponsor for clarification of this issue, the sponsor only required a confirmation that the subject was alive and/or had no graft loss to be considered as complete.

Dr. Rajagopalan

The inspection of Dr. Rajagopalan was completed, but I have not received the EIR as of this date. A Form FDA 483 was issued to Dr. Rajagopalan at the close of the inspection listing 8 inspectional observations which are detailed below. No response to the Form FDA 483 has been received. Deviations from the regulations (based upon the Form FDA 483) are as follows:

1. Failure to obtain informed consent in accordance with 21 CFR Part 50. [21 CFR 312.60]

   The informed consent of subject — was dated 9/27/95 although the transplant was performed 9/26/95.

2. Failure to ensure that an investigation is conducted according to the signed investigational plan (protocol). [21 CFR 312.60]

Eligibility

Although the protocol inclusion criteria specified that females capable of becoming pregnant must have a negative serum pregnancy test immediately prior to study entry, a pregnancy test was not performed on subject — until one day after the first dose of the investigational drug was administered.

Rejection Episodes

Subject — was treated for a rejection episode on 5/25/96 but a biopsy was not performed within 48 hours of treatment as required by the protocol. A biopsy performed on 5/31/96 was assessed as mild acute (grade 1) rejection.

Serious Adverse Events

Ten serious adverse events were reported to the sponsor beyond the protocol specified time frame. No documentation was available to indicate when the death of subject — was reported to the sponsor.

Electrocardiographic Evaluation

The protocol required that a baseline ECG be performed within 24 hours prior to the first dose of study medication. Subject — received the renal transplant on 11/21/95, however, the only ECG documentation was dated 2/13/95.

3. Failure to maintain adequate and accurate case histories. [21 CFR 312.62(b)]

There was no source documentation such as entries in the Medication Administration Record to verify that the investigational drug was actually administered for 5 out of 16 subjects reviewed as follows: subject — (1st dose), subject — (2nd dose), subject — (2nd dose), subject — (2nd dose). Other study records provided reference to the investigational drug administration, for example, medication ordered in the Physician's Order Sheet (subject —, 2nd dose) or notation in the Patient Information Log (subject —, 2nd dose), but did not document the actual investigational drug administration.

There was no pharmacy record of the time of investigational drug reconstitution to verify that the investigational drug was administered within its 2 hour expiration period.

The Transplantation Anaesthetics and Adjuncts case report forms for subjects ——— did not identify all medications (missing 1-4) used in the perioperative period.

Rejection Episode case report forms were not completed for subject — for the biopsies performed 5/15/96 and 5/31/96.

Two hospitalizations for subject — and 1 hospitalization for subject — were not reported in the respective case report forms.

Infections for subject — (1/18-20 and 1/25-27) and subject — (/13-15/96) were not reported in the Infections case report form. The 2/13-15/96 infection for subject — was recorded in the Hospitalization case report form.

4. Failure to promptly notify the Institutional Review Board (IRB) of subject death [21 CFR 312.66]

Study documentation indicated that the death of subject 168 which occurred on 1/6/96 was not reported to the IRB until 6/96.

BIMO Administrative Follow-up

There was no issuance of an FDA Form 483, Inspectional Observations, at the close of the inspections for Drs. Bennett and Kahan. Based upon our review of the EIRs for Drs. Bennett and Kahan no correspondence will be issued from CBER as a result of these inspections. The inspection of Dr. Bennett has been classified as "VAI", voluntary action indicated, and the inspection of Dr. Kahan has been classified as "NAI", no action indicated. The preliminary classification of the inspection of Dr. Rajagopalan, pending submission of the EIR, is "VAI" with the issuance of correspondence outlining the deviations noted during the inspection.

Should you have any questions or comments about the contents of this memo or any aspect of Bioresearch Monitoring, please contact me at (301) 827-6337.

Patricia E. Hasemann, D.V.M.

Attachment: FDA Form 483

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 60 8th Street NE Atlanta, GA 30309 (404) 347-3218	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Dr. P.R. Rajagopalan, MD	PERIOD OF INSPECTION 3/9-13/98	C. F. NUMBER
TITLE OF INDIVIDUAL Principle Investigator	TYPE ESTABLISHMENT INSPECTED Clinical Investigator	
FIRM NAME Dr. Rajagopalan/Med. Univ. of S.Carolina	NAME OF FIRM, BRANCH OR UNIT INSPECTED	
STREET ADDRESS 171 Ashley Ave. #404 Clinical Sciences Bldg.	STREET ADDRESS OF PREMISES INSPECTED	
CITY AND STATE (Zip Code) Charleston, SC 29425	CITY AND STATE (Zip Code) same	

DURING AN INSPECTION OF YOUR FIRM ~~I~~ (WE) OBSERVED:

(A REVIEW OF PROJECT SDZ CHI 621, STUDY NO. ——— WAS PERFORMED)

1) At least 10 Serious Adverse Event Reports (SAEs) were observed to have been reported to the sponsor beyond the protocol specified time frame, based on a comparison of the "Date of Report" and the faxed date. Included in this is # — who died 1/6/96 and there is no documentation available showing when the sponsor was notified. In addition, documentation indicated that this death was not reported to the IRB until June of 1996.
2) The Informed Consent of patient # — was dated 9/27/95, although the procedure was performed 9/26/95.
3) For the 16 subjects reviewed the following protocol deviations were observed:
   A) A pregnancy test was not performed on patient # — until 9/4/95 which was after the first dose was administered on 9/3/95.
   B) Rejection Episode forms were not completed for patient # — for biopsies performed 5/15/96 & 5/31/96.
   C) For patient # — a rejection episode resulted in treatment, however, a biopsy was not performed.
   D) For patient # — the initial ECG was performed greater than 24 hours prior to administering the drug; ECG was done approximatel 9 months earlier.
4) Source documentation (i.e. hospital records) to support the administration of the study drug could not be positively located for the following patients: (5 out of 16 reviewed) # — (1st dose), # — (2nd dose), # — (1st dose), # — (2nd dose), # — (2nd dose)
5) The Transplantation Anaesthetics and Adjuncts record in the following case report forms(CRFs) did not identify all (missing between 1 and 4) of the medications used during the perioperative period: # ———
6) No record was made of when the test article was reconstituted by the pharmacy, in order to verify that the article was in fact administered within its labeled 2 hour expiration period.
7) Two additional hospitalizations for pt.# — and one for pt.# — were not reported in the respective CRFs.
8) Infections went unreported for pt. — (1/18-20/96 & 1/25-27/96) and pt. — (2/13-15/96). (Note that patient — was recorded on the Hospitalization CRF for this 2/96 date) BTC 3/13/98

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Barbara Pritchard Janice L. King	EMPLOYEE(S) NAME AND TITLE (Print or Type) Barbara Pritchard Inv Janice L. King, Investigator	DATE ISSUED 3/13/98

FORM FDA 483 (5/85) PREVIOUS EDITION MAY BE USED. INSPECTIONAL OBSERVATIONS PAGE 1 OF 1 PAGES